170. Polarographic Properties and Electrochemical Reduction of 1,2-Dimethyl-3-indolyl Heteroaryl Ketones

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Summary

The reduction of a series of 1,2-dimethyl-3-indolyl heteroaryl ketones, where the heteroaryl components are 2-benzoxazolyl, 2-benzothiazolyl, 1-methyl-2-benzimidazolyl, 4- and 2-pyridyl, in aprotic and protic solution are described by means of DC. and AC. polarography, cyclic voltammetry and coulometry.

In acetonitrile a two-step reduction mechanism with a reversible first and an irreversible second one-electron transfer has been observed, confirmed by AC.-polarographic and cyclovoltammetric measurements. The reduction potentials, between -1.377 and -1.787 V for the first step, and between -1.937 and -2.250 V (*vs.* Ag/AgCl) for the second, could not be correlated with the LUMO energies from HMO calculations which was explained as being due to a distorted configuration of the π systems.

In protic media (ethanol/water) reduction occurs in an irreversible one-step mechanism. Measurements of the pH dependence of the half-wave potential in the pH* range 0–12 and the evaluated transfer coefficients show that the reduction step represents the transfer of two electrons and two protons yielding secondary alcohols and no dimerization products under any condition. These findings are supported by coulometric and macroscale electrolysis of the ketones; the products isolated were characterized by IR. and ^{1}H-NMR. data.

Introduction. – Reviewing the results about the polarographic and electrochemical reduction of alkylaryl- and diaryl ketones **1** [1], one may say that in protic solution the reduction proceeds to the products **2**, **3** and **4** *(Scheme)*, depending upon the pH, the concentration, the electrode material and its potential. Electrochemical reduction *e.g.* of benzophenone on a mercury surface of controlled potential yields only benzopinacol **2** at pH 1.3 (the radical mechanism of which has been supported by a number of polarographic findings [2]) and mainly benzhydrol **3** at pH 8.6 [3]. In strongly acidic conditions reduction progresses to the diphenylmethane **4** [4].

At the dropping mercury electrode (DME.) below pH 6 benzophenone shows two cathodic waves which are superimposed in basic solution [5]. Systematic investigation of substituted benzophenones at the DME. has revealed a limited

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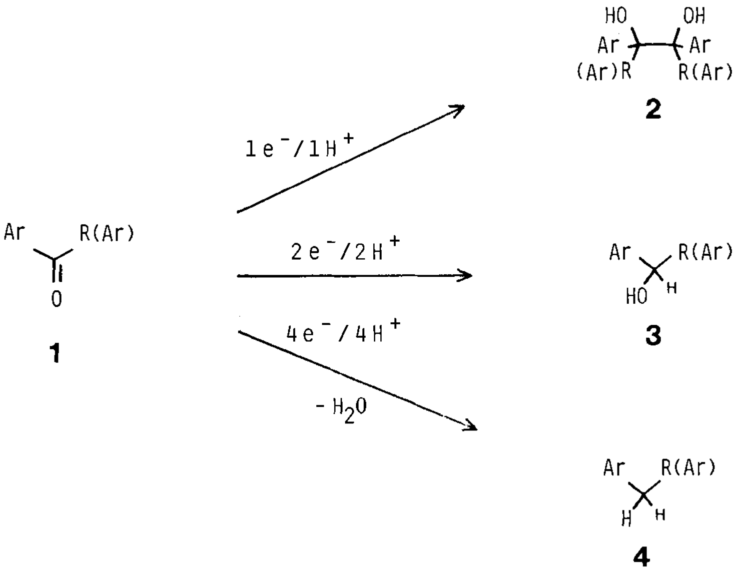
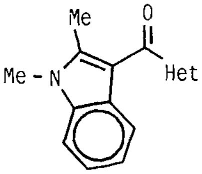


correlation between *Hammett* substituent constants and half-wave potentials at various pH conditions [1d].

Little is known about the effects of replacing a benzene group by a heteroarene on the polarographic and electrochemical behaviour of aromatic ketones. Studies of the alkyl heteroaryl ketones with π-excess heteroaryl functions such as 2-acetylfuran [6] and -thiophene [7] have proved that electro reduction in acidic aqueous solution on a mercury surface [6] and in dimethylformamide on a tin electrode [7] yields the hydrodimerization product analogous to **2**, whereas the π-deficient systems 4- [8] and 2-acetylpyridine [9] exhibit the contradictory result that the former gives the pinacol **2** and the latter the alcohol **3** under strongly acidic conditions. The investigation of the pH dependence of the product ratio **2**/**3** in the case of 2-acetylpyridine, however, shows that complete pinacolization is achieved in basic media.

Analogous investigations in the field of diheteroaryl ketones have not yet been undertaken. In the present paper we discuss the polarographic behaviour of the series of indolyl heteroaryl ketones **5** [10] in aprotic and protic solution and their coulometric and macroscale electrolysis in protic conditions.



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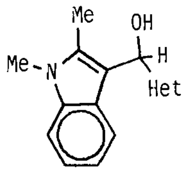
Het=
A: 2-benzoxazolyl
B: 2-benzothiazolyl
C: 1-methyl-2-benzimidazolyl
D: 4-pyridyl
E: 2-pyridyl



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Polarographic investigation. – *Measurements in acetonitrile.* Aromatic ketones such as benzophenone form highly stable radical anions when reduced in aprotic solvents [11]. Higher electrode potentials yield less stable dianions which are obtained by stepwise reduction *via* the radical anion [11]. The results with the ketone series **5 A–5 E** are analogous *(Table 1).*

Two well-resolved waves were found with a half-wave potential difference of 0.5–0.6 V. The slopes $\alpha \cdot n$ indicate a reversible one-electron reduction at the less negative first wave and an irreversible one-electron step at the second. This is confirmed by a comparison of the half-wave potentials from DC. polarography with the peak potentials obtained from the AC.-polarographic voltage sweep [12] *(Table 1):* the deviations of the peak potentials E_{AC} from the half-wave potentials $E_{1/2}$ are negligible with respect to the first waves. The second peaks however were shifted distinctly to more negative voltages than their corresponding half-wave potentials, their peak current also being much lower and their half width greater compared with the first peak [11] (see *Fig. 1*).

Table 1. *Polarographic data of ketones* **5A–5E** *in acetonitrile with 0.1*M *tetrabutylammonium perchlorate (TBAP) at 25°, t = 0.6 s.* ($E_{1/2}$: half-wave potential (±0.002 V, *vs.* Ag/AgCl – 3.5M KCl), α: transfer coefficient (±0.02), i_D/c_0: diffusion current, E_{AC}: peak potential from AC. polarography, E_{LUMO}: LUMO eigenvalue from HMO calculations)

Compound	$-E_{1/2}$ [V]	α	i_D/c_0 [A · cm^3/mol]	$-E_{AC}$[V]	$-E_{LUMO}$ [β]
5A	1.447	1.01	2.33	1.446	0.254
	1.963	0.45	0.66	2.044	
5B	1.377	1.03	2.30	1.380	0.297
	1.937	0.74	2.32	1.958	
5C	1.755	1.01	2.60	1.752	0.326
	2.248	0.46	2.26	2.314	
5D	1.632	1.00	2.44	1.630	0.362
	2.250	0.35	2.44	2.328	
5E	1.787	1.02	1.51	1.790	0.369
	–	–	–	–	

5A: 1,2-Dimethyl-3-indolyl 2-benzoxazolyl ketone.
5B: 1,2-Dimethyl-3-indolyl 2-benzothiazolyl ketone.
5C: 1,2-Dimethyl-3-indolyl 1-methyl-2-benzimidazolyl ketone.
5D: 1,2-Dimethyl-3-indolyl 4-pyridyl ketone.
5F: 1,2-Dimethyl-3-indolyl 2-pyridyl ketone.

In *Figure 1A* the DC. and AC. polarograms of **5B** are shown as an example. Further evidence of the reversibility of the first electron transfer and the irreversibility of the second emerges from the cyclic voltammetry measurements *(Fig. 1B):* the first reduction step produced an almost ideally symmetrical shape (peak potentials – 1.41 and – 1.34 V respectively), whereas the second (with a peak at – 2.02 V in the reducing direction) exhibited no reoxidation signs at all. Final evidence of a one-electron transfer at the potential of the first wave was supplied by the coulometric reduction of **5B** at a potential slightly above the first half-wave, yielding a deep violet dye after 'addition' of one electron per molecule which was

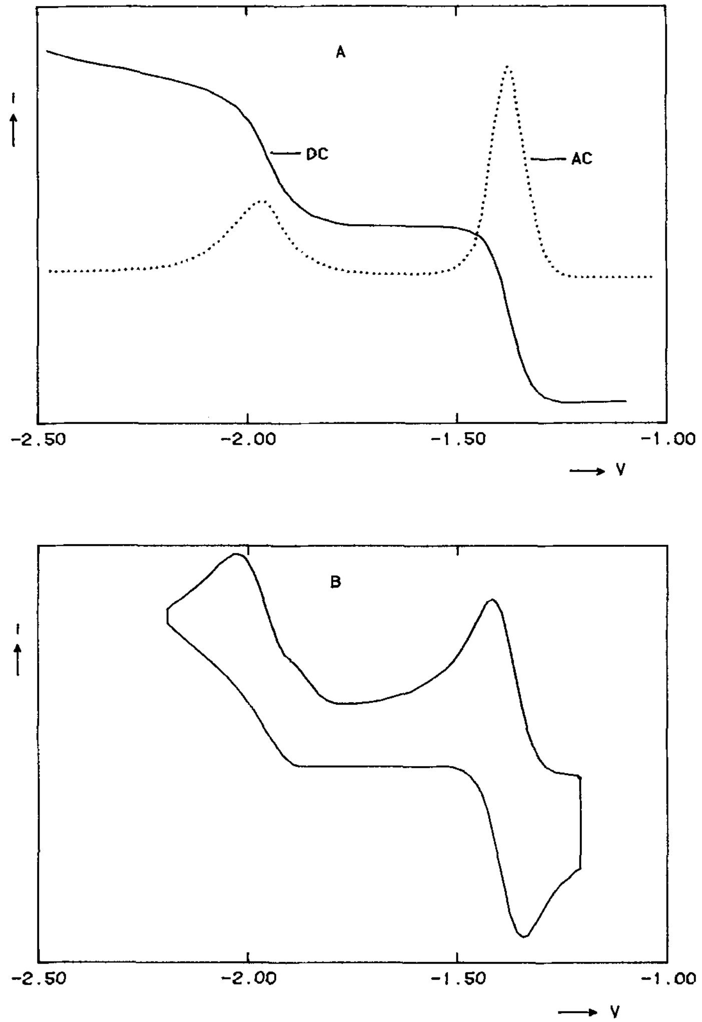

Fig. 1. A) *DC. and AC. polarograms of* **5B**. B) *Cyclic voltammogram of* **5B** ($2.776 \cdot 10^{-4}$M in acetonitrile, 0.1M TBAP, Hg *vs.* Ag/AgCl–3.5M KCl; A: t = 0.6 s, B: t = 2 s, scan rate: 4 V/s)

extremely sensitive to air. The reduction-air-oxidation cycle could be repeated several times without any fading owing to side reactions which proves its reversibility.

Generally there is a linear relationship between the energy of the lowest unoccupied molecular orbital (LUMO) of the π system to be reduced and its reduction half-wave potential [13] *(equ. 1)*. The LUMO eigenvalues of ketones **5** are calculated on the HMO basis using a parameter set which was adjusted to the parameters for many-electron computations [14].

$$\varepsilon_{\text{LUMO}} = -E^{\text{red}}_{1/2} + C \tag{1}$$

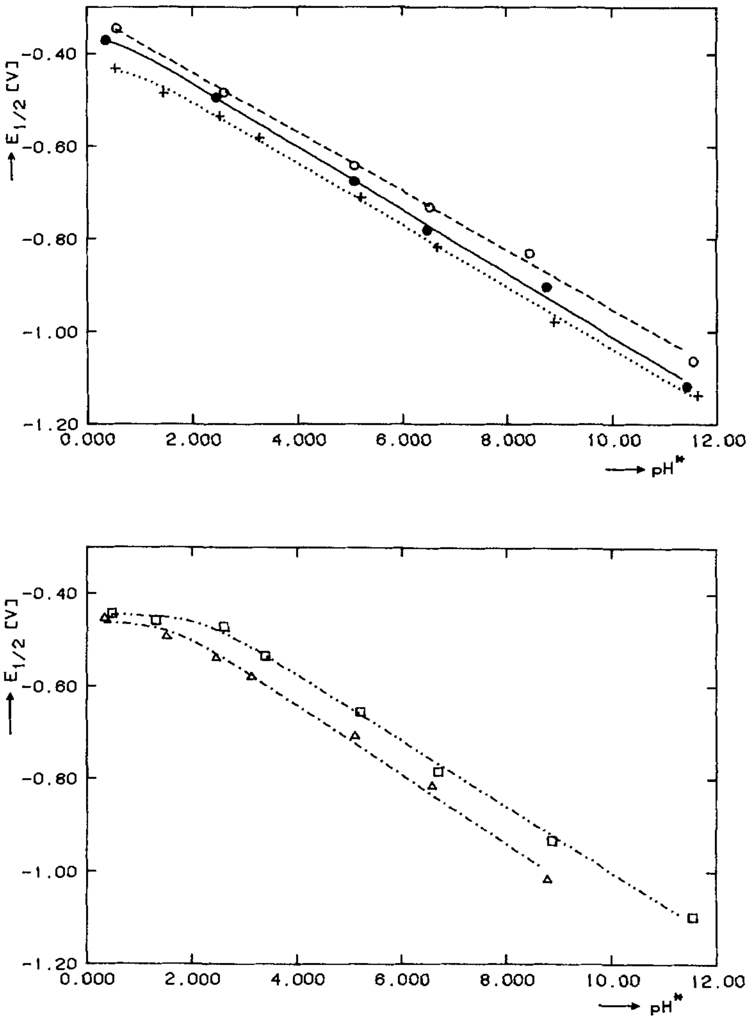

Fig. 2. *Variation of half-wave potentials* $E_{1/2}$ *with pH* of ketones* **5A–5E** *in water/ethanol* (1:1 *v/v*)
5A: ●——, **5B**: ○– – –, **5C**: △–·–·–, **5D**: □–··–··–, **5E**: +·······

The resulting values, collected in the last column of *Table 1*, reflect to some extent the increasing basicity of the varied heteroarenes on going from **5A** to **5E**. However the correlation with the first half-wave potential is very poor (r = 0.767). Apart from the uncertainties inherent in the parameters, the inadequacy of this correlation might at least partly be ascribed to variously distorted configurations of the π-systems; as the HMO calculations revealed a strongly bonding interaction between the carbonyl carbon and the varied heteroaryl group in the LUMO, any twisting of this heteroarene out of the plane of the remaining system will destabilize the LUMO to a remarkable degree. (Twisting of the bond between the carbonyl and the indole group has no comparably strong influence on the LUMO eigenvalue because of a very weak interaction in this orbital.)

Measurements in ethanol/water. For reasons of solubility of the ketones **5** in pure water, the voltammetric investigations were carried out in water/ethanol (1:1 *v/v*). Over the whole pH* range [15] only one well defined cathodic wave could be observed, the half-wave potential of which becomes more negative with increasing pH* for all ketones under investigation *(Fig. 2)*.

Except for **5C** and **5D** the pH* dependence of $E_{1/2}$ is nearly linear over the measured range. The *Brønsted* basicity of the 2-benzimidazolyl and 4-pyridyl fragments in **5C** and **5D** however is high enough to move the dissociation constant of their acid-base equilibrium into the scanned pH* sphere. For a system with rapidly established acid-base equilibrium prior to the irreversible electrode reaction, the dependence of the half-wave potential on the pH* is given by *Equation 2* [16], where C is a function of the heterogeneous rate constant k_h of a chemical reaction preceding the electrode process proper, drop time t and diffusion coefficient D, and K represents the acid-dissociation constant.

$$E_{1/2} = \mathrm{C}(k_\mathrm{h}, \mathrm{t}, \mathrm{D}) + \frac{\mathrm{RT}}{\alpha \mathrm{nF}} \cdot \ln \frac{[\mathrm{H}^+]}{K + [\mathrm{H}^+]} \qquad (2)$$

From a least-square fit of the measured results to *Equation 2* pK* values of 1.60 ± 0.36 for **5C** and 2.18 ± 0.23 for **5D** were calculated.

It remains to prove the irreversibility of the polarographic reduction. The slopes RT/αnF of the polarographic waves at $E_{1/2}$ give values for the product $\alpha \cdot$ n between 1 and 2. AC.-polarographic investigations showed a distinct shift of the peak potentials compared with $E_{1/2}$, varying between 10 and 40 mV to lower potentials. The differences were found to be greater the smaller $\alpha \cdot$ n, in accordance with the theoretical predictions [12]. The absence of any peak potential in the reverse voltage-sweep step observed in the cyclic voltammetry measurements under all pH* conditions at a scan speed of 4 V/s-analogous to the irreversible second step in acetonitrile *(Fig. 1B)* – is clear proof of the irreversible character of the electrode reaction. As the transfer coefficient α cannot exceed 1.0 it follows that the number n of transferred electrons is always greater than 1. This was confirmed by the coulometric investigations (next paragraph).

Electrochemical reduction. – Electrochemical reduction of benzophenone and its substituted derivatives in aqueous solution yields various products (**2**, **3** or **4**) with correspondingly different consumption of electrons depending on the pH conditions [1] [3] [5]. In contrast, when ketones **5** were subjected to the same electrolytic reaction under analogous conditions the number of electrons consumed in the process always remained 2 per molecule in the applied water/ethanol mixture, independent of the pH*.

These coulometric statements have been supported by the isolation of the products from a macroscale electrolysis and their characterization (^{1}H-NMR., *Table 2*). The only product extracted in high yields in every case was alcohol **6**. The stability of **6D** towards reoxidation was, however, very poor. An originally colourless ethereal solution of **6D** turned yellow within minutes. A thin-layer-chromatographic analysis showed the formation of a single yellow product which was identified as ketone **5D** by chromatographic comparison. Alcohol **6C** was identified by direct comparison with the product obtained from the addition of 1-methyl-2-lithiobenzimidazole to 1,2-dimethylindole-3-carbaldehyde [10].

Lack of the strong carbonyl absorption peak (1613–1630 cm^{-1} in the IR. spectra of ketone **5** [10]) in the reduction products proved that the electrolytic hydrogenation took place at the expected functional group. Furthermore the appearance of a strong broad absorption band in the range of 3170–3440 cm^{-1}, attributable to an O–H-stretching vibration, indicates the formation of an alcohol. The hydrogen bound to the C-atom of the CHOH-group appears well separated in the ^{1}H-NMR. spectra *(Table 2).*

Table 2. *Proton signals of the alcohols* **6A–6D**[a]) *from ^{1}H-NMR. measurements in $CDCl_3$* (internal standard: tetramethylsilane)

Proton Position	Number	Chemical shift [ppm] (multiplicity[b]))			
		6A	**6B**	**6C**	**6D**
H_3C–N(1)	3	3.63 (*s*)	3.65 (*s*)	3.62 (*s*)	3.66 (*s*)
H_3C–C(2)	3	2.50 (*s*)	2.25 (*s*)	2.42 (*s*)	2.41 (*s*)
HOCH–C(3)	1	6.30 (*s*)	6.44 (*s*)	6.24 (*s*)	6.12 (*s*)
HOCH–C(3)	1	3.48 (br. *s*)	–	4.92 (br. *s*)	3.06 (br. *s*)
H_3C–N[c])	3			3.31 (*s*)	
H–C(2,6)[d])	2				8.44/ 8.49 (*d*)
aromat. H	8 (**6D**: 6)	6.9–7.8 (*m*)	6.7–8.4 (*m*)	6.8–7.4/ 7.7–7.9 (*m*)	6.9–7.4 (*m*)

[a]) Compound **6E** not available due to instability.
[b]) Multiplicities: *s* = singlet, *d* = doublet, *m* = multiplet.
[c]) H_3C–N of the benzimidazolyl moiety.
[d]) H–C(2,6) of the pyridyl moiety.
6A: (1,2-dimethyl-3-indolyl)-(2-benzoxazolyl)methanol.
6B: (1,2-dimethyl-3-indolyl)-(2-benzothiazolyl)methanol.
6C: (1,2-dimethyl-3-indolyl)-(1-methyl-2-benzimidazolyl)methanol.
6D: (1,2-dimethyl-3-indolyl)-(4-pyridyl)methanol.

Conclusion. – Comparing the polarographic properties of ketones **5** in acetonitrile and ethanol/water, it is evident that the half-wave potentials are shifted drastically to less negative values in protic solution. Moreover the two separated waves in the aprotic medium corresponding to two consecutive one-electron reduction steps combine to a single two-electron wave in the presence of accessible protons. The pH dependence of the half-wave potentials indicates a proton addition preceding or simultaneous with the electrode reaction. These findings and the bend in the $E_{1/2}$-pH* plot of **5C** and **5D** *(Fig. 2)* reproduced by *Equation 2* are consistent with the following scheme:

$$AH^+ \rightleftarrows A + H^+ \qquad \text{I}$$

$$AH^+ + 2\,e^- \rightarrow AH^- \qquad \text{IIa}$$

$$AH^- + H^+ \rightarrow AH_2 \qquad \text{III}$$

The rapidly established equilibrium (step I) is followed by the electrode reaction (step IIa). The irreversible step III may succeed the reduction process or progress simultaneously.

The systems which show a straight $E_{1/2}$-pH* plot *(Fig. 2)* probably have pK* values lying below the measured pH* range. The original basic centre in step I need not be the carbonyl function but may be the N-atom of the varied heteroaryl group. Step IIa might then contain a simultaneous or consecutive proton exchange from the nitrogen to the carbonyl oxygen, as in IIb.

$$AH^- + H^+ \rightleftarrows HA^- + H^+ \qquad \text{IIb}$$

The observed dependence of $E_{1/2}$ on the pH* remains thereby unaffected. The only hint that primary protonation (step I) occurs at the heteroaryl N-atom is given by the fact that the pK* value of the 4-pyridyl derivative **5D** is the highest, reflecting the greatest distance of the basic centre from the carbonyl substituent which exhibits a strong (–M)-effect on its immediate neighbour atoms (compare the pK of 2- and 4-acetylpyridine with 2.81 [17] and 3.51 [18] respectively).

HMO calculations on the present ketone series do not allow for such drastic pK differences if the carbonyl functions are assumed to be the *Brønsted* bases and the minute differences of the π-electron density on their oxygen atoms are considered.

Experimental Part

Apparatus. AC.- and DC.-potential current curves were obtained on a *Polarecord E506* with an electrode stand *E505* from *Metrohm* Herisau. Cyclic voltammetry measurements were carried out with the help of an attached *VA Scanner E612 (Metrohm)* and recorded on a storage oscilloscope *5111/2.5A15N* from *Tektronix*. The dropping mercury electrode was operated with a flow speed of 1.1 mg/s, a platinum sheet serving as the auxiliary electrode in the anodic solution consisting of acetonitrile/0.1M tetrabutylammonium perchlorate TBAP, for acetonitrile measurements) and 1M aqueous KNO_3 (for water/ethanol measurements) respectively.

A *Coulostat E524* with *Integrator E525 (Metrohm)* was used for coulometric investigations. Reductions in acetonitrile were performed on a platinum net cathode EA240, whereas in protic media, a mercury pool, covering the bottom of the reaction vessel, connected to the circuit by means of the free tip of a glass-coated platinum wire and stirred by an immersed teflon-coated magnetic bar, was used as working electrode. A graphite pin electrode *EA 274/2* formed the anode. Throughout, the reference electrode was an Ag/AgCl electrode *EA 427* in a 3.5M aqueous KCl.

A *MINC 11-BD* computer from *Digital Equipment Corp.* was used for the evaluations, drawing of curves and molecular formulae.

Chemicals. Solvents used for polarographic and coulometric measurements were commercial ethanol and acetonitrile *(Uvasol)* from *Merck*. TBAP *(Fluka)* was purified by recrystallization from ethanol/ether before use. The preparation of ketone **5** is described elsewhere [10].

Polarographic and cyclovoltammetric procedure. Buffered ethanol/water mixtures were prepared by dilution of a doubly concentrated aqueous *Britton-Robinson* buffer solution [19] with an equal amount of an ethanolic solution of the ketones (stock concentrations *ca.* 500 mM) and addition of 0.1M NaCl to smooth the differences of the ionic strength at the various pH* values. For pH* values lower than 2 a mixture of 2N and of 0.2N H_2SO_4 with an equal volume ethanol was used. Exact pH* values were measured with a glass electrode and are corrected for its surface potential difference in the applied mixture compared with pure water by an additive term of 0.18 [20].

Solutions of acetonitrile contained 0.1M TBAP as supporting electrolyte; concentrations of $3.62–7.98 \cdot 10^{-4}$M in ketones **5** were measured. Oxygen-free conditions were achieved by flushing highly pure N_2 (type *50*, *Carba*) through the solutions *ca.* 15 min prior to and maintaining a slow flow during the measurements. An AC. voltage of 6 mV without phase shift was superimposed on the potential sweep for the AC.-polarographic investigations.

Coulometric and macroscale electrolysis. Sufficient mercury to cover the bottom of the electrolysis cell, forming a cathode area of 7 cm^2, and the buffer solution consisting of either 1M KOH, 1M HCl or 0.8M CH_3COONa in ethanol/water 80:20, were added to the test cell. The magnetic bar, half-immersed in the mercury pool, stirred both mercury and solution while O_2 was removed by N_2. Prior to the addition of the ketones, the solution was electrolyzed at a cathode potential *ca.* 0.3 V more negative than that at which the ketone reduction was to be run until the ground current maintained a constant value of less than 2 mA. The ketones (*ca.* 0.2 mM) were then added as solids, dissolved and the reduction started at the appropriate potentials to achieve 'half times' of 10 to 30 min. The reduction process was complete when the previous ground current was reached.

The number of electron equivalents needed for the reduction of the ketones was evaluated by a least-square fit of the observed progress of the current at constant potential to *equation 3* where Q_t is the number of equivalents at time t, Q_∞ the final number of equivalents, C_1 the reaction rate and C_2 represents the ground current.

$$Q_t = Q_\infty (1 - e^{-C_1 t}) + C_2 t \tag{3}$$

For macroscale electrolytic reductions 0.7-0.8 mM ketones were treated analogously. After completion of the reduction the solution was diluted with water, the product extracted with ether and the ethereal phase washed carefully before evaporization to dryness. The white residue proved to be pure by thin layer chromatography except for **6E** which reoxidized quickly. The following m.p. were recorded: **6A** (cubes) 156°, **6B** (plates) 127°, **6C** (needles) 218°, **6D** (needles) 147°.

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